

REMARKS

By this amendment Claims 9-11 and 21-50 are in the application.

Reconsideration of the patentability of the application is respectfully requested in view of the following remarks.

In accordance with the Examiner's request a formal Figure 4A is provided as approved by the Examiner and is submitted herewith with an accompanying Letter to the Official Drafter.

Amendment is made to the specification on page 6 to delete the term "in a fixed orientation" and found objectionable by the Examiner. This amendment is made to advance prosecution of this application and reduce issues for consideration by the Examiner rather than having Applicants traverse the objection. It is respectfully submitted that the specification as originally filed makes it quite clear that the specimen is held in a fixed orientation by the clamp including the various different disclosed embodiments of clamps. The fact that a specimen is fixed does not necessarily imply that it cannot be moved through some force impressed by an operator. Amendment is further made to the claims to remove this term and employ terminology clearly present in the application as originally filed.

Claims 9-11, 21-24 and 30-35 were rejected under 35 U.S.C. §112, first paragraph. The rejection is overcome by the amendment of Claims 9, 21, and 30.

The prior art has been considered by the Applicants, but is respectfully submitted that the combinations of references cited by the Examiner fail to render obvious the subject matter of Applicants' claims. At the outset, it should be noted that it is the Examiner who bears the initial burden, on review of the prior art or any other ground, of presenting a prima facie case of unpatentability. If the examination at the initial stage does not produce a prima facie case of unpatentability then without more the applicant is entitled to grant of the patent, see in this regard *In re Oetiker et al.*, 24 USPQ 2nd 1443-4 (Fed. Cir. 1992). The Examiner is also respectfully reminded that the factual inquiry, whether to combine references must be searching and thorough. It must be based on objective evidence of record. Furthermore, and case law makes it clear, that the best defense against the sole, but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirements for a showing of the teaching or

motivation to combine prior art references. It is submitted respectfully as will be shown below that the Examiner has failed to show that there has been a rigorous application of this requirement in combining of the references. The Examiner has combined multiple references using Applicants' specification as a roadmap without any indication in the references themselves suggesting their combination. It is therefore respectfully submitted that the rejection of the claims for obviousness under 35 USC §103 should be withdrawn.

Claim 9 as now amended is directed to an apparatus for imaging excised tissue having a refractive index. A tray is provided upon which excised tissue of at least several millimeters in thickness is disposed. The tray includes a window. The apparatus further includes means for clamping the excised tissue upon the tray to keep the tissue stationary and against the window. Support for this language may be found in the specification at page 7, lines 5-9. Optics are directed towards the window and the excised tissue for imaging the tissue through the window. Additionally, the tray contains an immersion medium having a refractive index, matching the refractive index of the excised tissue. Claim 9 stands rejected under 35 USC §103 as being unpatentable over the combination of Connelly (U.S. Patent No. 3,510,194) in view of Ornstein (U.S. Patent No. 4,545,831).

Connelly is directed to a receptacle for microporous filter membranes used for examining particulate matter in fluids. Clamp members 44 are associated with a cover member or lid for holding down the filter 41 to a floor to prevent electrostatic attraction of the filter to the cover member. Imaging of the filter is made through the cover member or lid, see in this regard discussion in this reference starting at column 2, line 3. The receptacle in Connelly is used for the imaging of particulates on the filter. The contaminants are contained on the filter membrane, which is held a sufficient distance from the window, such that external contaminants on the window are out of focus with respect to the contaminants of interest. Connelly's goal is to be able to precisely and reliably count the particles on the membrane filter, see column 1, lines 47-49. In order to precisely and reliably count the particles, it is apparent that one would want to make the particles as visible as possible to the optical instrument viewing the particles. Adding an index matching fluid with substantially the same refractive index as the particles reduces or eliminates the light scatter from the particles just as a glass rod inside a glass becomes less visible when the glass is filled with water (or oil). Thus the refractive index

matching described by Ornstein would reduce the visibility of the particles intended for imaging in Connelly. It is thus apparent that Connelly teaches away from imaging the sample specimen through a window against which the specimen is clamped and furthermore the combination of Connelly taken with Ornstein would not be considered to be of any suitability to one of ordinary skill in the art because the combination would render Connelly inoperative. Furthermore, Ornstein is directed to a method for handling fragile tape-supported thin sections of tissue specimens to enable transport of such sections onto microscope slides. The thin sections of tissue are cut by a microtome and are probably of the order of several microns in thickness. There is no indication in this reference of use of a tray having an immersion medium which has a refractive index matching the refractive index of the excised tissue and which is used to image excised tissue of at least several millimeters in thickness as is claimed in Claim 9. Thus Claim 9 is submitted to be patentable over the combination of Connelly taken with Ornstein.

Claim 10 was rejected as being unpatentable over the combination of Connelly taken with Ornstein under 35 USC §103 and additionally was rejected as being unpatentable over Connelly in view of Ornstein and further in view of Tomimatsu (U.S. Patent No. 5,870,223). The impropriety of combining Connelly with Ornstein has been noted above in view of the lack of motivation for combining these references as such combination tends to lead to inoperative embodiments. Tomimatsu is directed to a microscope for liquid immersion observation wherein a pouch is associated with a sealed container containing the immersion liquid. Tomimatsu further discloses that the pouch 14 includes a second liquid that has substantially the same refractive index as the immersion liquid. As noted above, the use of such liquids in the combination that includes the teachings of Connelly would provide inoperative embodiments in view of the fact that such liquids would tend to obscure the specimen of Connelly. Thus, there is no motivation for combining these three references as they also lead to inoperative embodiments. Furthermore, Tomimatsu teaches away from use of a clamp to keep the tissue stationary and against a window. The specimen in this reference is merely shown immersed in the liquid and not clamped against a window as being claimed in Applicants' Claim 10. Thus, the Examiner has selectively picked and chosen isolated teachings of each of these references using Applicants' specification as a roadmap to support rejection

under 35 USC §103. The rejection of Claim 10 is thus respectfully submitted to be based on hindsight and inappropriate.

Claim 11 is a dependent claim of Claim 9 and stands rejected under 35 USC §103 as being unpatentable over Connelly in view of Ornstein and further taken with Atwood et al. The inappropriateness of combining Connelly with Ornstein has been discussed above. Atwood et al. (U.S. Patent No. 5,675,700) is directed to an in situ PCR (polymerase chain reaction) for amplification of nucleic acids contained in a prepared cell or tissue sample. In the process of Atwood et al., cells or tissue are first placed on the slide that has been treated to cause the cells or tissue to stick to the slide and not be washed off or floated away by the aqueous reagents of the PCR process or the subsequent treatments for visualization of the amplified DNA. A volume of PCR reagent covers the sample and a thin impermeable membrane is sealed over the sample by mechanically pressing the perimeter of the membrane next to the slide with a clamp. To provide for the in situ process, this assembly is heated to close to the boiling point of the solutions and then cooled. The cycle is repeated several times. Because the solutions are heated to close to the boiling point, the membrane is flexible to dissipate the pressure of the liquid on the slide.

It is apparent that the sample is not retained on the slide by the cover. The cover just provides a chamber to hold the reagents for the PCR reaction. The cover is concave away from the specimen both to hold the drop of reagent prior to sealing and to form a small reservoir of liquid over the specimen. The sample 12 is next to the slide whereas the reagent 13 is filling the space. It is apparent that it is not desirable in Atwood for the cover or any clamp to contact the specimen, such contact can distort the morphology of the tissue specimen (see column 4, line 15). It is further apparent that the reservoir needs to have sufficient volume to tissue surface ratio to provide adequate reagent concentration of the specimen to sustain the PCR reaction. Thus, the Atwood et al. invention teaches away from a flexible cover or clamp for retaining the excised tissue against the surface. The only pertinent discussion in Atwood et al. relative to viewing of the sample may be found in column 6, lines 14-16 wherein it is noted that the amplified sample on the slide is viewed in a conventional manner through a microscope **after** the cover and its retainer have been removed. Thus, the combination of Connelly taken with Ornstein and Atwood

et al. is also inappropriate as one of ordinary skill in the art would not consider the teaching of Atwood et al. pertinent to use of a tray for the viewing of specimens.

Claim 21 is an independent claim directed to an apparatus for imaging excised tissue having a refractive index. The apparatus includes a tray upon which the excised tissue is to be disposed for imaging. The tray includes a window upon which the excised tissue is adapted to be supported. A clamp includes a finger for clamping the excised tissue to hold the tissue stationary and against the window. Optics are directed towards the excised tissue in the window for imaging the excised tissue through the window. The tray contains an immersion medium having a refractive index, matching the refractive index of the excised tissue. Claim 21 stands rejected as being unpatentable over the combination of Connelly taken with Ornstein under 35 USC §103. The rejection of Claim 21 is also respectfully traversed. As noted above there is no motivation for the combination of these two references as placement of an immersion liquid in the container of Connelly would render the system in Connelly inoperative as tending to render less visible the specimen being observed. Furthermore, Connolly teaches of imaging through the top cover, and not through a window upon which the excised tissue is adapted to be supported. Thus, it is respectfully submitted that Claim 21 is also patentable as the Examiner has failed to set forth a prima facie rejection of Claim 21.

Claim 22 is a dependent claim of Claim 21 and adds the feature that the finger has a spring biasing the finger **to hold the excised tissue** upon the tray. Claim 22 was rejected as being unpatentable over Connelly in view of Ornstein and further in view of Hauser (U.S. Patent No. 4,159,875). Hauser is directed to a slide holder for use in an automated differential blood cell classifier. The Examiner cites Hauser as disclosing a specimen holder with a spring biasing a finger. However, the finger in Hauser is biased to urge the glass slide 20 in the direction of a lip 15. This is merely to retain the slide within the holder 10 and has nothing to do with the retaining of an excised tissue upon the tray to which Claim 22 is directed. For this reason, it is respectfully submitted that the Examiner has also failed to set forth a prima facie rejection of Claim 22.

Claim 23 is a dependent claim of Claim 9 and adds the feature that the clamping means has a mesh capable of holding the excised tissue upon the tray. Claim 24 is a dependent claim of Claim 9 and adds the feature that the clamping means has a

membrane capable of holding the excised tissue upon the tray. Claims 23 and 24 stand rejected as being unpatentable over the combination of Connelly taken with Ornstein and further in view of Foote (U.S. Patent No. 1,002,910). The inappropriateness of combining Connelly with Ornstein has been noted above as leading to inoperative embodiments. Foote is directed to a display mount for exhibiting natural history specimens wherein a specimen 19 is placed on a pliable sheet 10 which causes the specimen to be held against a glass cover of the mount. It will be noted that this is a display mount and one not disclosed as being suited for use for imaging of excised tissue. Furthermore, the stated purpose of holding the specimen on the pliable sheet is noted in the specification of Foote on page 2, lines, 15-20 as being for purposes of shipment and not as providing any utility for imaging of an excised specimen. It is thus again respectfully submitted that the Examiner has impermissibly used Applicants' specification to create a hindsight reconstruction of the prior art. Thus, Claims 23 and 24 are submitted to be patentable over the combination of Connelly taken with Ornstein and Foote.

Claim 25 is an independent claim directed to a holder for support of excised tissue during imaging of the excised tissue. The holder comprises a container having a window upon which the excised tissue is adapted to be disposed and a clamping member in the container capable of restraining the excised tissue in a position with respect to the window. The excised tissue is imaggable through the window. Claim 25 stands rejected as being unpatentable over Atwood et al. under 35 USC §102. The Examiner cites this reference as being pertinent to a holder for use in imaging an excised tissue. This interpretation of Atwood et al. is respectfully traversed. Atwood et al. has been discussed in great length above and it is submitted that Applicants have made it convincingly clear that there is no disclosure of a holder in this reference for support of an excised tissue during imaging. The holder in Atwood et al. has been shown to be for purposes of an in situ PCR reaction and after such reaction imaging is accomplished by removing the reaction product from the holder for imaging in the usual way. There is further no disclosure in this reference of a clamping member for restraining the excised tissue in position against the window as is being claimed in Claim 25.

Claim 25 also stands rejected as being unpatentable over Connelly taken with Tomimatsu under 35 USC §103. As noted above, Connelly is directed to a filter mount

wherein pins are provided upon a cover of the mount to prevent the filter from curling. Imaging of the particles on the filter takes place through the cover 40 and not through the surface upon which the filter is pressed against. Tomimatsu is also discussed above and is directed to a microscope system for liquid immersion observation, wherein the specimen is generally floating in the immersion liquid. There is no teaching in this combination of references of a holder for support of excised tissue during imaging wherein the clamping member restrains the excised tissue in a position against the window for imaging. Thus, it is respectfully submitted that the Examiner has failed to also make a prima facie case of anticipation or obviousness of Claim 25 and thus the rejections of Claim 25 should also be reversed.

Claim 26 is a dependent claim of Claim 25 and should also be patentable for the same reasons described above for Claim 25.

Claim 27 is a dependent claim of Claim 26 and is directed to a spring that biases the finger to restrain the excised tissue against the window. Claim 27 is submitted to be patentable and not anticipated by Atwood et al. for the same reasons provided above for Claim 25.

Claim 27 also stands rejected as being unpatentable over the combination of Connelly taken with Tomimatsu and further in view of Hauser. The obviousness rejection of Claim 27 is also respectfully traversed. Hauser is cited by the Examiner for the teaching of a specimen holder wherein a glass slide is held in position in a holder by integral springs 13a and 13b which bias the glass in the direction of a lip 15. As noted above, this is not a teaching of a spring that biases the finger to restrain the excised tissue against the window as set forth in Claim 27. Therefore, it is respectfully submitted that Claim 27 is patentable over the combination of Connelly taken with Tomimatsu and Hauser.

Claim 28 is a dependent claim of Claim 25 and adds the feature that the clamping member comprises a mesh capable of restraining the excised tissue in a position against the window. Claim 29 is a dependent claim of Claim 25 and is directed to a clamping member that comprises a membrane capable of restraining the excised tissue in a position against the window. Claims 28 and 29 stand rejected as being unpatentable over the combination of Connelly taken with Tomimatsu and Foote. The rejection of claims 28

and 29 are also respectfully traversed. Foote, as noted above, is directed to an exhibition holder for exhibiting natural history specimens and discloses a pliable sheet that supports the natural history specimen against a glass forming a part of the holder. There is no indication in this reference of providing a holder for excised tissue for use for purposes of imaging. The purpose of supporting the specimen in Foote is to facilitate transportation of the specimen, presumably to prevent it from rattling against the glass. The selection of Foote in combination with Connelly and Tomimatsu could have only been suggested by Applicants' specification. There is no teaching in any of these three references of providing a holder wherein urging of excised tissue against the window is provided for purposes of imaging. Thus, the rejection of claims 28 and 29 should also be reversed.

Claim 30 is directed to a method for imaging excised tissue. The container is provided having a surface for placement of the tissue. The tissue is restrained in the container against the surface to keep the tissue stationary and against the surface. Then imaging of the tissue is made through at least a part of the surface against which the tissue is held. Claim 30 stands rejected as being anticipated under 35 USC §102 by Atwood et al. As noted in great detail above there is no disclosure in Atwood et al. of a method of imaging an excised tissue sample having the steps set forth immediately above. There is no teaching at all in Atwood et al. of an imaging method that uses a holder. The holder described in Atwood et al. is merely used for a PCR reaction and following such reaction the reaction product is removed from the holder. Imaging of the material is made in the usual course using a microscope after removal from the reaction chamber and that is the sole description relative to imaging in Atwood et al. Thus Atwood et al. cannot be said to anticipate Claim 30 and this rejection should be withdrawn.

Claim 30 also stands rejected as being unpatentable over the combination of Connelly in view of Tomimatsu under 35 USC §103. As noted above, Connelly is directed to filter mount wherein pins are provided upon a cover of the mount to prevent the filter from curling. Imaging of the particles on the filter takes place through the cover 40 and not through the surface upon which the filter is pressed against. Tomimatsu is also discussed above and is directed to a microscope system for liquid immersion observation wherein the specimen is generally floating in the immersion liquid. There is no teaching

in this combination of references of a method of imaging of excised tissue wherein the excised tissue is held stationary against the surface and imaging is made of the tissue through at least a part of the surface against which the tissue is held. Thus, it is respectfully submitted that Claim 30 is also patentable over the combination of Connelly taken with Tomimatsu.

Claim 31 has now been amended to be dependent upon Claim 30 and also should be patentable as not being anticipated by Atwood et al. nor being rendered obvious by the combination of Connelly taken with Tomimatsu under 35 USC §103. Claim 31 is directed to the imaging method of Claim 30 and wherein the restraining step is carried out with the aid of a clamping member located within the container. Atwood et al. as noted above does not even disclose imaging of excised tissue on a container. As noted above, Connelly discloses imaging of particles through a different surface than that which is claimed in Claims 30 and 31 and Tomimatsu does not suggest otherwise. Similarly, Claims 32 and 33 are dependent claims of Claim 31 and should also be patentable as not being anticipated by Atwood et al. and not being rendered obvious by any combination of prior art cited in the prosecution of this application.

Claim 34 is directed to defining the restraining step of Claim 30 as being carried out with the aid of a mesh in the container. Claim 35 is directed to defining the restraining step of Claim 30 as being carried out with the aid of a membrane in the container. Claims 34 and 35 are dependent claims of method Claim 30 and stand rejected as being unpatentable under 35 USC §103 over Connelly in view of Tomimatsu and Foote. All of these references have been discussed in great detail above, it being noted that Connelly fails to teach a method of imaging through a surface against which an excised tissue sample is being held, indeed no tissue sample is disclosed in Connelly. Tomimatsu is directed to imaging a sample that is floating in the immersion liquid. Foote does not teach anything about imaging excised tissue sample; nor does this reference teach anything about excised tissue samples. The reference merely teaches of an exhibition holder for natural history specimens and a pliable sheet that is used to retain the sample in the holder to facilitate transport thereof.

Newly submitted Claims 36-50 are directed to methods, a tray system and an imaging system including a tray system where different types of trays are used for

different types of tissues. Support for this subject matter may be found in the specification at page 6, first full paragraph. It is respectfully submitted that the prior art relied upon by the Examiner also fails to teach or render obvious the subject matter of Claims 36-50.

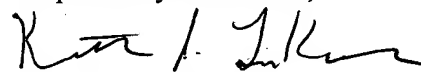
In Applicants' response dated September 25, 2002 to the Office Action of July 31, 2002 request was made of the Examiner to confirm that certain references listed on the Information Disclosure Statement have been considered. It is further requested that confirmation be provided to Applicants that a newly issued patent identified in the Supplemental Information Disclosure System submitted with the response dated September 25, 2002 has also been considered by the Examiner.

Applicants further provide, via electronic submission concurrently herewith, a second Supplemental Information Disclosure Statement of prior art for consideration by the Examiner.

For the above reasons it is respectfully submitted that all the claims now in the application are allowable and that the application may be passed to issue, prompt notice of which is earnestly solicited. If, contrary to expectations, questions shall remain, the undersigned may be called for a telephone interview in order to advance prosecution of the application towards allowance. A petition for a three-month extension of time is enclosed.

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Respectfully submitted,



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